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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/674,462	05/08/2001	Robert Ian Lechler	2292/OH795	8594
7590	12/08/2005		EXAMINER	
King & Spalding 191 Peach Tree Atlanta, GA 30303			OUSPENSKI, ILIA I	
			ART UNIT	PAPER NUMBER
			1644	

DATE MAILED: 12/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	09/674,462	LECHLER ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	ILIA OUSPENSKI	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 28 September 2005.
- 2a) This action is FINAL.                    2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1,5-7 and 31-52 is/are pending in the application.
- 4a) Of the above claim(s) 7,31-34,51 and 52 is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 1,5,6,35-39,41-47 and 50 is/are rejected.
- 7) Claim(s) 40,48 and 49 is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All    b) Some \* c) None of:
  1. Certified copies of the priority documents have been received.
  2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ . |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)               |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>5/25/2001</u> . | 6) <input type="checkbox"/> Other: _____ .  |

## DETAILED ACTION

1. Applicant's amendment/remarks, filed 09/28/2005, are acknowledged.

Claims 2 – 4 have been cancelled.

Claims 8 – 30 have been cancelled previously.

Claims 6, 7, and 42 have been amended.

*Claims 1, 5 – 7, and 31 – 52 are pending.*

Claim 7 has been withdrawn from consideration by the Examiner as being drawn to nonelected inventions.

2. Applicant's election of Group I (Claims 1, 5, 6, 35 – 41, and 43 – 50, drawn to a biological reagent comprising porcine CTLA-4) in the reply filed on 09/28/2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim 42, as amended, is rejoined with Group I.

Claims 31 – 34 and 51 – 52 are withdrawn from consideration by the Examiner as being drawn to nonelected inventions.

***Claims 1, 5, 6, and 35 – 50 are under consideration in the instant application.***

3. Applicant's amendment to the specification, filed 09/28/2005, is acknowledged. The instant application, as amended, appears to be in sequence compliance for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

4. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in the United Kingdom on 04/30/1998. It is noted, however, that applicant has not filed a certified copy of the above application as required by 35 U.S.C. 119(b).

If the International Bureau is unable to forward a copy of the certified priority document to the U.S. Patent and Trademark Office because applicant failed to comply with PCT Rule 17(a)-(b), then applicant is required to provide a certified copy of the priority document during the national stage to fulfill the requirement of 37 CFR 1.55(a)(2). See MPEP 1893.03(c).

5. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the claims are directed*.

6. The abstract of the disclosure is objected to because of the use of legal phraseology. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. Correction is required. See MPEP § 608.01(b).

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7. Applicant's IDS, filed 05/25/2001, is acknowledged, and has been considered.

Reference No. 2 has been considered, but lined through, as it is not appropriate for printing on the face of a Patent.

8. The use of trademarks has been noted in this application (e.g. pBluescript on page 17). Each letter of the trademarks should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

9. Claim 49 is objected to because of the following informalities: the sequence identifier is in improper format. Applicant is reminded that the proper format of sequence identifiers is "SEQ ID NO:". Appropriate correction is required.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112.

*The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

11. Claims 1, 38, and 46 are rejected under **35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 1 is indefinite in the recitation of "co-stimulatory signal 2," because the metes and bounds of the claimed invention are unclear. The specification discloses at page 2, lines 12 – 14, that signal 2 is supplied by the interaction between B7 molecules on the antigen-presenting cells and CD28 on T-cells. However, one of ordinary skill in

the art would be aware that other molecular interactions are also known in the art to mediate secondary costimulatory signals, such as those of ICOS with ICOS-L and of PD-1 with PD-L1 and PD-L2. Therefore, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention.

B. Claims 38 and 46 are indefinite in the recitation of "wherein the immunoglobulin gamma is human C $\gamma$ 1," because "C $\gamma$ 1" lacks proper antecedent basis in the recitation of "immunoglobulin." The designation "C $\gamma$ 1" apparently refers to the constant region of the heavy chain of the  $\gamma$ 1 subtype of IgG; therefore, the recitation reads as "immunoglobulin is a part of an immunoglobulin," and as such, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

*The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

13. Claim 1 is rejected under **35 U.S.C. 112, first paragraph**, because the specification, while being enabling for a biological reagent comprising porcine CTLA-4 that inhibits rejection of a xenotransplanted organ in pigs, does not reasonably provide enablement for a generically recited biological reagent comprising porcine CTLA-4 that inhibits rejection of a xenotransplanted organ. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not provide a sufficient enabling description of the claimed invention.

A person of skill in the art is not enabled to make and use the claimed biological reagent commensurate with the scope of the claims as presently recited, because it was well known in the art at the time the invention was made that the efficacy of biological reagents depends on the species of the subject. While CTLA4-Ig has been found to be effective in inhibiting transplant rejection when administered to the animal of the same species as the source of CTLA4 (e.g. Kurlberg et al., Scand. J. Immunol., 2000, 51: 224 – 230; see entire document, in particular, e.g. Introduction at pages 224 – 225 and references cited therein), it is highly unpredictable whether the porcine CTLA4 would be effective when administered to species other than pig. For example, Drew et al. teach that a biological reagent comprising murine CTLA4 was not effective when administered to sheep, presumably because ovine CTLA4 binds murine B7 molecules less efficiently than its murine counterpart (Vaccine, 2001, 19: 4417 – 4428; see entire document, in particular, e.g. pages 4426 second column – 4427 first column). Therefore, Applicant does not provide a sufficiently enabling disclosure regarding how to make and use the claimed biological reagent that inhibits rejection of xenotransplanted organs, as generically recited.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, the efficiency of porcine CTLA4 in other species is unpredictable; thus the experimentation left to those skilled in the art, is unnecessarily, and improperly, extensive and undue.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

*(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.*

15. Claims 1, 5, 6, 35 – 38, 41 – 46, and 50 are rejected under **35 U.S.C. 102(e)** as being anticipated by Larsen et al. (US Patent 5,916,560; see entire document).

Larsen et al. teach a method for inhibiting an immune response resulting in graft rejection, by contacting a B7-positive cell with a soluble ligand having at least a portion of the extracellular domain of CTLA4, and optionally a portion of an immunoglobulin molecule, such as Cy1 (see entire document, in particular, column 8 line 26 – column 9 line 27). Larsen et al. teach that the method can be practiced in pigs, and a number of other animal species (e.g. column 8 lines 40 – 45). Since it is well known in the art that therapeutic polypeptides, to be effective, have to originate from the species being treated, inherent in the teachings of Larsen et al. is the disclosure of porcine CTLA4 and its Ig fusions for inhibiting graft rejection. Since the same protein is taught by Larsen et al. as is presently claimed, its amino acid sequence is inherently the same.

Therefore the reference teachings anticipate the instant claimed invention.

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16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

*(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 5, 35, 39, 41, 43, and 47 are rejected under **35 U.S.C. 103(a)** as being unpatentable over Larsen et al. (US Patent 5,916,560; see entire document) in view of Strom et al. (US Patent 6,165,476; see entire document).

Larsen et al. have been discussed *supra*, and teach fusion polypeptides comprising porcine CTLA4 and immunoglobulin.

Larsen et al. do not teach fusion polypeptides wherein a linker connects the porcine CTLA4 to the immunoglobulin.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to connect two parts of a fusion protein via a linker, because a

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person of ordinary skill in the art was well aware of the advantages of using linker sequences. For example, Strom et al. teach that connecting members in a fusion protein by a flexible linker can increase biological activity, and provide working examples of such linkers (see entire document, in particular, e.g. Background and Summary at columns 1 – 3 and the Table at columns 4 – 5). In view of these teachings, one of ordinary skill in the art at the time the invention was made would have been motivated to connect the members of porcine CTLA4-Ig fusion protein or Larson et al. via a linker, and have a reasonable expectation of success in doing so.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

18. Claims 40, 48, and 49 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

**19. Conclusion: claims 40, 48, and 49 appear to be directed to allowable subject matter.**

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILIA OUSPENSKI whose telephone number is 571-272-2920. The examiner can normally be reached on Monday-Friday 9 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ILIA OUSPENSKI

Patent Examiner

Art Unit 1644

December 5, 2005



PHILLIP GAMBEL, PH.D

PRIMARY EXAMINER



